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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/594,097	05/06/2008	Ulrich Hersel	13907-00007-US (CPX64383P	8928

23416 7590 01/17/2012

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EXAMINER	
WESTERBERG, NISSA M	

ART UNIT	PAPER NUMBER
1618	

MAIL DATE	DELIVERY MODE
01/17/2012	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/594,097	HERSEL ET AL.	
	Examiner	Art Unit	
	NISSA WESTERBERG	1618	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 October 2011*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

5)☒ Claim(s) *89-128* is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) *89-128* is/are rejected.

8)☐ Claim(s) _____ is/are objected to.

9)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

12)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *9/13/11*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicants' arguments, filed October 11, 2011, have been fully considered but they are not deemed to be fully persuasive. The following rejections and/or objections constitute the complete set presently being applied to the instant application.

Claim Rejections - 35 USC § 112 - 1st Paragraph

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claim 122 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection. There was no disclosure in the application as originally filed of a pyrimidine ring as that aromatic group Ar, the structure added to claim 122 in the amendments to the claims filed October 11, 2011.

If Applicant is in disagreement with the Examiner regarding support for the amended claim, Applicant is respectfully requested to point to page and line number wherein support may be found for the instant invention.

Claim Rejections - 35 USC § 112 - 2nd Paragraph

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 90, 92, 98, 101 - 113 and 115 - 124 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The variables R2 and Y5 are not defined in this claim. These variables are defined in the specification but not in the claims. Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

6. Claims 93, 94 and 114 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 93 and 94 recite the limitation "biologically active moiety" while the independent claim recites “amine-containing biologically active moiety”. There is insufficient antecedent basis for this limitation in the claim and it is unclear if any biologically activity moiety will meet the limitation of claims 93, and 94, which could also cause these claims to be improper dependent claims. Proteins will contain at least one amino group at the N-terminus, but it is possible to have nucleic acids (e.g., a single stranded polyU) and vaccines (e.g., nicotine vaccines)

that do not contain an amine group so it is unclear if the amine-containing limitation carries over to these dependent claims or if those limitations have been dropped due to the change in how this piece of the polymeric cascade prodrug or corresponding linker reagent is being referenced. Similarly, claim 114 recites the “the active moiety”. Please clarify.

7. Claim 114 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 89 can be either the prodrug itself or a linker reagent that can be used to prepare a prodrug, and as the “T” in the formula of claim 8 can be either an amine containing biologically active moiety or a leaving group. Claim 114 requires that the active moiety comprises a leaving group - it is unclear if the leaving group must be present in the active moiety in the final prodrug or if the leaving group in the active moiety as the corresponding linker reagent can leave when the active moiety is attached to the carrier to produce the polymeric cascade prodrug. Please clarify.

8. Claim 125 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The variable Y6 is defined in the fourth line from the end of the claim but it does not appear in any of the formulas or definitions given in the claims. The variables R2 and R6 are present in the formula but are not defined. Formula IIb also contains only a circle with no information regarding the chemical structure of this portion

of the molecule, such as the "Ar" used to indicate that this is the aromatic ring portion as in formula II in the same claim. Please clarify.

9. Claim 128 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. There is no active step (e.g., administering of the prodrug to a subject) so that the in vivo cleavage can occur, but there is no step in the claim that provides for getting the prodrug according to claim 89 into a subject for in vivo cleavage to occur.

Claim Rejections - 35 USC § 112 - 4th Paragraph

10. The following is a quotation of the fourth paragraph of 35 U.S.C. 112:

> Subject to the [fifth paragraph of 35 U.S.C. 112], a claim in dependent form shall contain a reference to a claim previously set forth and then specify a further limitation of the subject matter claimed. A claim in dependent form shall be construed to incorporate by reference all the limitations of the claim to which it refers.

11. Claims 93 and 94 are rejected under 35 U.S.C. 112, 4th paragraph, as being of improper dependent form for failing to further limit the subject matter of the claim upon which it depends, or for failing to include all the limitations of the claim upon which it depends. Claim 89, from which claims 93 and 94 depend, has been amended to require an amine-containing biologically active moiety. While most of the items recited in the Markush group of claim 94 would contain at least one amine group, some vaccines are based on small molecules such as nicotine that do not contain an amine group. And

a single stranded polyU polyribonucleotide will not contain any amine groups. Therefore, the Markush group of claims 93 and 94 encompasses biologically active moieties that do not contain amine groups. Applicant may cancel the claim(s), amend the claim(s) to place the claim(s) in proper dependent form, rewrite the claim(s) in independent form, or present a sufficient showing that the dependent claim(s) complies with the statutory requirements.

Improper Markush Group

12. Claims 89, 91, 94 - 97, 114 and 126 - 128 are rejected on the judicially-created basis that it contains an improper Markush grouping of alternatives. See *In re Harnisch*, 631 F.2d 716, 721-22 (CCPA 1980) and *Ex parte Hozumi*, 3 USPQ2d 1059, 1060 (Bd. Pat. App. & Int. 1984). The improper Markush grouping includes species of the claimed invention that do not share both a substantial structural feature and a common use that flows from the substantial structural feature. **The members of the improper Markush grouping do not share a substantial feature and/or a common use that flows from the substantial structural feature for the following reasons**: The formula contains a masking group; a carrier, which can be anything and need not even be polymeric, as it can be the corresponding linker reagent for a polymeric cascade prodrug and not necessarily the prodrug itself; and the variable T, either an amine-containing biologically active moiety or a leaving group, and in particular leaving group is alrge and highly diverse genus. None of these pieces results in a members of the Markush group that

share a substantial structural feature. In response to this rejection, Applicant should either amend the claim(s) to recite only individual species or grouping of species that share a substantial structural feature as well as a common use that flows from the substantial structural feature, or present a sufficient showing that the species recited in the alternative of the claims(s) in fact share a substantial structural feature as well as a common use that flows from the substantial structural feature. This is a rejection on the merits and may be appealed to the Board of Patent Appeals and Interferences in accordance with 35 U.S.C. §134 and 37 CFR 41.31(a)(1) (emphasis provided).

Claim Rejections - 35 USC § 101

13. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

14. Claim 128 is rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd.* v. *Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

Claim Rejections - 35 USC § 102

15. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

16. Claims 89, 91, 94, 95, 97 and 114 are rejected under 35 U.S.C. 102(b) as being anticipated by Rhee et al. (US 5,510,121).

Rhee et al. discloses polyethyleneglycol modified with an activated group on one or more ends of the molecule so that covalent binding can occur between the PEG and the free amino groups (a leaving group) on the glycosaminoglycan (GAG, col 16, ln 17 onward). For example, the difunctional PEG succinimidyl (S-PEG) forms an ester linkage that hydrolyses under physiological conditions wherein one GAG is a masking group, one GAG is T, a biological active moiety (see col 17), and the disclosed GAGs of hyaluronic acid, chondroitin sulfate, dermatan sulfate, chitosan, keratan sulfate, keratosulfate and heparin all contain amine groups (col 7 - 9) and the PEG is the carrier. Cytokines or growth factors can be conjugated to polymers like as the GAG-synthetic polymer-cytokine (col 5, ln 7 - 21). The disclosed cytokines or growth factors include interferons, tumor necrosis factors (TNFs) and colony stimulating factors (CSFs) (col 12, ln 7 - 22).

Note that claim 95 is a product-by-process claim and the process by which the cytokine or growth factor was prepared does not patentably distinguish the claimed

product. "[E]ven though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process." *In re Thorpe*, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed. Cir. 1985) (citations omitted) **MPEP 2113**.

17. Claims 89, 91 and 94 - 97 are rejected under 35 U.S.C. 102(b) as being anticipated by Polonelli et al. (Infect Immun, 2003).

Polonelli describes decapeptides synthesized using solid phase peptide synthesis employing Fmoc chemistry (p 6206, col 1, ¶ 1). The peptide is the carrier, the Fmoc is a leaving group and MBHA solid support resin is a masking group. The decapeptides are fragments of recombinant single chain fragment variable (KT-scFv), which reads on a fragment of an antibody.

Claim Rejections - 35 USC § 103

18. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

19. The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

20. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

21. Claims 89, 91, 93, 94, 97, 114 and 126 - 128 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rhee et al. (US 5,510,121).

Rhee et al. discloses polyethyleneglycol modified with an activated group on one or more ends of the molecule so that covalent binding can occur between the PEG and the free amino groups (a leaving group) on the glycosaminoglycan (GAG, col 16, ln 17 onward). For example, the difunctional PEG succinimidyl (S-PEG) forms an ester linkage that hydrolyses under physiological conditions wherein one GAG is a masking

group, one GAG is T, a biological active moiety (see col 17), and the disclosed GAGs of hyaluronic acid, chondroitin sulfate, dermatan sulfate, chitosan, keratan sulfate, keratosulfate and heparin all contain amine groups (col 7 - 9) and the PEG is the carrier. Cytokines or growth factors can be conjugated to polymers like as the GAG-synthetic polymer-cytokine (col 5, ln 7 - 21). The disclosed cytokines or growth factors include interferons, tumor necrosis factors (TNFs) and colony stimulating factors (CSFs) (col 12, ln 7 - 22). The conjugates can be used in a wide range of therapeutic applications such as dermal wound healing or cardiovascular applications, or injectable drug systems (col 5 ln 22 - 35).

Rhee et al. does not explicitly hydrolyze the conjugates in vitro or administer the conjugates.

It would have been obvious to the person of ordinary skill in the art at the time the invention was made to administer the conjugate to provide the therapeutic effects of the conjugate as these conjugates have therapeutic usefulness only when administered. When these conjugates with esters that hydrolyses under physiological conditions are exposed to physiological conditions (either in vitro such as by administration to a subject or a solution of physiological pH, such as about pH 7.4), the ester will hydrolyze and the amine-containing moiety will cleave from the prodrug by means of a substantially non-enzymatic reaction.

Note that claim 95 is a product-by-process claim and the process by which the cytokine or growth factor was prepared does not patentably distinguish the claimed product. "[E]ven though product-by-process claims are limited by and defined by the

process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process." *In re Thorpe*, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed. Cir. 1985) (citations omitted) **MPEP 2113**.

22. Claims 99 and 100 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rhee et al. as applied to claims 89, 91, 93, 94, 97, 114 and 126 - 128 above, and further in view of Tasaka et al. (WO 03/028765; all citations from the US 2004/0254197, the PGPub of the national stage application).

Rhee et al. is discussed above.

Rhee et al. does not disclose conjugation to the specific drugs or classes recited in claims 99 and 100.

Tasaka et al. discloses covalent conjugates of PEG to drug, X, wherein one or two molecules of drug can be bound to PEG, but the bond between the drug and PEG is slowly broken down (¶¶ [0009], [0014] - [0020]). The chemical structure of the drug is not limited and can be anti-inflammatories, antimicrobials, drugs that improve blood flow (which reads on cardiovascular drugs and/or vasodilators), analgesics or antitumor drugs such as doxorubicin hydrochloride (¶ [0022]).

It would have been obvious to the person of ordinary skill in the art at the time the invention was made to use drugs as those disclosed by Tasaka et al. in the conjugates

of Rhee et al. The person of ordinary skill in the art would have been motivated to make those modifications and reasonably would have expected success because both relate to drug-polymer conjugates and Tasaka disclose that drugs such as doxorubicin or analgesic can be conjugated for therapeutic use in subjects. The selection of the agent depends on the particular condition being treated and the drug(s) which have therapeutic effects.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to NISSA WESTERBERG whose telephone number is (571)270-3532. The examiner can normally be reached on M - F, 8:00 a.m. - 4 p.m. ET.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael G. Hartley can be reached on (571) 272-0616. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Nissa M Westerberg/
Primary Examiner, Art Unit 1618